A case of marked alveolar bone augmentation after chemotherapy in a pediatric patient with acute lymphocytic leukemia

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Introduction

Oral symptoms are often the first manifestation of leukemia in children, and there are many reports of tooth extraction for abnormalities such as tooth movement. Leukemia accounts for 38% of all childhood cancers in Japan, followed by brain tumors (16%), lymphomas (9%), and neuroblastomas (AML) (8%), and the remaining 5% are unknown. Among the types of acute lymphoblastic leukemia (ALL), B-cell acute lymphoblastic leukemia (B-ALL) accounts for 80–85% and T-cell acute lymphoblastic leukemia (T-ALL) about 10–15%.[1]

Marukawa et al. reported that approximately 20–35% of leukemia patients have initial symptoms in the oral cavity, and it is not uncommon for oral symptoms to appear early in the course of leukemia. The most common oral symptoms in leukemia patients are gingival hemorrhage and gingival swelling, followed by jawbone abnormalities such as miconus hypersensitivity, alveolar bone resorption, and tooth movement, and many cases of leukemia have been detected in the oral cavity.[2-8]

Curtis et al. reported a correlation between leukemia and mild or worsening jaw bone symptoms in pediatric patients with ALL, based on radiographic studies of jaw bone changes. However, there are no reports of cases of jaw bone resorption in patients with ALL in Japan, although there are a few reports of cases in which jaw bone resorption was observed due to leukemia cell infiltration following the onset of leukemia. No cases have been reported in which the jawbone was severely resorbed.[9, 10]

In this study, we report a case of a pediatric patient with ALL who developed leukemia and had significant jaw bone resorption due to infiltration of leukemia cells, resulting in severe tooth movement and the inability to properly occlude the jaw.

Case history and examination

A 14-year-old male patient first presented to the clinic on Oct 12th, 2021, with gingival hemorrhage and full-maxillary tooth movement, leading to feeding difficulties. His family history and medical history were unremarkable. Earlier in late September 2021, he had noticed bilateral mandibular molar tooth movement and gingival swelling around the molars. Despite occlusal adjustment by a local dentist, the symptoms did not improve, the gingival swelling spread to the entire jaw, and he began to bleed easily. Later, due to tooth movement and worsening gingival bleeding, he had difficulty with oral intake and presented to our department for examination and treatment in late October.

Upon clinical examination, the patient had a body temperature of 37.4°C, signs of fatigue, and a relatively lean body condition (height, 162 cm; weight, 38.5 kg; body mass index, 14.7 kg/m^2). He reported that he could only take soft food orally.

He had pain in both knees, elbows, and shoulder joints. Scattered petechial hemorrhagic patches were observed on the dorsal surfaces of his feet and abdomen (Fig 1), and his liver and spleen were enlarged on palpation.

His face was symmetrical. His maxillary and mandibular gingiva were bleeding, erythematous, and swollen (Fig 2A), with significant tooth movement observed in all jaws (Table 1A) and uneven occlusion of the bilateral molars.

Differential diagnosis, investigations, and treatment

The panoramic radiograph imaging findings conducted on Oct 12, 2021, showed significant alveolar bone resorption in the upper and lower jaws, and the alveolar hard line, mandibular canal wall, and trabecular structure were indistinct (Figs 3A). Blood test results showed that the white blood cell count was increased to 15900/μl, and other blood cell counts were decreased. In addition, blasts were observed in the peripheral blood, and C-reactive protein, lactate dehydrogenase, and ferritin levels were elevated, suggesting leukemia. A bone marrow examination was then performed to confirm the diagnosis.

Bone marrow biopsy: a diagnosis of B-ALL was made for this patient, with 75.8% of the lymphoblasts being medium to large in size and showing high nucleus/cytoplasm ratio vacuoles. The oral lesions were then attributed to the clinical diagnosis: alveolar bone resorption due to leukemic cell infiltration in B-ALL (Fig 4).

Treatment and course

On the day of admission, IA4 remission induction therapy (vincristine 1.5 mg/m^2 intravenous injection: days 1, 8, 15, 22, and 28; daunorubicin 30 mg/m^2 intravenous infusion: days 1, 8, 15, and 22; L-asparaginase 5000 U/m^{2}intravenous infusion: days 5, 8, 11, 14, 17, 20, 23, and 26; methotrexate 12 mg bone marrow injection: days 5 and 26; cytarabine 30 mg bone marrow injection: days 5 and 26) was started according to the ALL-B12 protocol. However, the patient was not cleaning his oral cavity due to fear of tooth movement and general malaise, and his oral hygiene thus worsened. Therefore, the department continued to provide oral care during chemotherapy. Induction therapy IA4 was designed to decrease leukemia cells, alleviate symptoms, and help achieve remission. The bone marrow biopsy performed on the 14th day after the start of IA4 showed that the lymphoblasts had disappeared and the patient's gingiva had improved with the disappearance of swelling and redness. The patient underwent remission induction therapy IA4 and was in remission on day 43 of the induction therapy. On day 54, after induction therapy IA4, he was started on early intensification therapy IB (cyclophosphamide 1000 mg/m^2 intravenous infusion: days 1 and 29; cytarabine 75 mg/m^2 intravenous injection: days 3–6, 10–13, 17–20, and 24–27; methotrexate 12 mg bone marrow injection: days 10 and 24; cytarabine 30 mg bone marrow injection: days 10 and 24; mercaptopurine 60 mg/m^2 oral administration: days 1-28) to prevent relapse after remission and to further decrease the number of leukemia cells. During this period, mucositis was observed in the oral cavity, probably due to chemotherapy, but no tooth movement was observed. Fifty-three days after the start of early intensive therapy IB, a bone marrow examination showed that the patient was still in remission, and intensive therapy was started to eradicate leukemia cells and prevent relapse. An oral examination and imaging were performed 9 days after the start of intensified therapy and 116 days after the start of treatment for leukemia.

Outcome and follow-up

All tooth movement, gingival hemorrhage, and gingival swelling resolved or improved, with no abnormalities in occlusion(Fig 2B). Periodontal pockets were less than 3 mm in all jaws (Table 1B). Bone growth was observed on panoramic radiographic findings in the area of significant alveolar bone resorption, and the alveolar hard line, mandibular canal wall, and bone beam structure, which had been unclear, became clear. On day116 after the start of treatment, in the mandibular left molar, which had been significantly resorbed,

the jawbone, which had been seen up to about one-third of the root apex at the initial examination, had grown up to the tooth cervix (Fig 3B).

Discussion and Conclusions

Compared to adults, children have a higher proportion of leukemias such as ALL and acute myeloid leukemia, followed by brain tumors, lymphomas, neuroblastomas, and other malignant tumors.[11, 12]

Among all malignant tumors in children, leukemia accounts for 38.4%, ALL for 70%, and BCP-ALL for 80–85% of cases.

In general, fever, hemorrhage, and anemia are the three major initial signs of acute leukemia. Other findings include enlarged lymph nodes, skin symptoms, hepatosplenomegaly, and neurological symptoms, which vary according to the type of disease.

Takagi et al. and Marukawa et al. reported that approximately 20–35% of patients with leukemia had oral symptoms as the initial manifestation, indicating that leukemia with an oral origin is relatively common. Therefore, it is important to accurately understand the oral symptoms of leukemia in patients and to always include it in the differential diagnosis of oral diseases.[13, 14]

The main oral symptoms that occur in patients with leukemia include gingival hemorrhage, gingival swelling, hypersensitivity, jawbone abnormalities, and tooth movement,[3-8, 13, 14] pointing to the importance of oral lesions in the diagnosis of acute lymphocytic leukemia.[15]

The patient in the present case was seen by a previous dentist because of marked swelling and pain of the gingiva, tooth movement, and alveolar bone resorption. However, when the patient returned to the dentist's office four weeks later, the inflammatory lesions, which were thought to be periodontitis, had spread further and worsened over the entire jaw, and thus the patient was referred to our department. At first presentation at our department, the patient's general condition was characterized by mild fever and malaise, and the periodontal tissue showed inflammatory findings that had no improvement.

Confirmation of bone marrow blasts by tests is effective in the diagnosis of leukemia.[16] However, Okamoto et al. reported a case in which the patient did not show typical oral symptoms and was in poor general condition; therefore, the diagnosis of periodontal disease, including the possibility of leukemia, should be made with more careful consideration.[5]

When leukemia is severe, oral symptoms become more severe and oral intake becomes difficult, which results in the deterioration of nutritional status and the general condition. Therefore, it is important to provide adequate oral care during the treatment of leukemia in affected patients to prevent secondary oral infections and deterioration of their general condition.

To identify the cause of the jawbone abnormalities associated with ALL, Takada et al.[17] performed site-specific autopsies of the mandible in 21 patients with leukemia and evaluated the presence of leukemia cell infiltration, which was confirmed in the mandibular bone marrow and gingiva (n=21), alveolar bone marrow (n=19), periodontal ligament (n=19), and dental pulp (n=20). These results showed that leukemic cell infiltration into the mandible begins in the jaw bone marrow and subsequently invades the alveolar bone and then the supporting tissue of the teeth. It is thought that leukemia cells infiltrate the mandible, starting from the jaw bone marrow, then invade the alveolar bone, which is the supporting tissue of the tooth, and subsequently invade and proliferate into the periodontal ligament and pulp. Therefore, it is highly likely that patients with leukemia first develop symptoms in the jawbone, which is infiltrated by leukemia cells, followed by tooth movement and gingival abnormalities due to the infiltration of leukemia cells into the surrounding tissues of the teeth, and finally by the infiltration of leukemia cells into the dental pulp, resulting in symptoms in the teeth.

However, in the present case, the clinical symptoms showed a clear systemic abnormality rather than local disease in the oral cavity, so a gingival biopsy was not performed to avoid the risk of spreading the disease.[18]

Additionally, the panoramic radiographic examination in this case showed a high degree of jaw bone resorption, and we considered it highly likely that the tooth movement and alveolar bone resorption were caused by infiltration of leukemia cells into the jaw bone, as previously reported.

Leukemia is a malignant hematologic tumor that develops mainly in the bone marrow, resulting first in bone destruction. In children with ALL, bone mineral loss is sometimes observed from the time of diagnosis, and this is due to a decrease in bone formation markers such as type I procollagen, C-terminal propeptide, and bone alkaline phosphatase, as well as an increase in bone resorption by parathyroid hormone-related peptide secreted by the leukemia cells, a decrease in 1,25(OH)2D3, and hypercalciuria, and the destruction of the sea-level chamber by leukemic cell infiltration.[19, 20]

There have been many reports of bone destruction due to leukemia cell infiltration in leukemia patients, even in organs other than the jawbone, and when the leukemia cell infiltration was cured by remission therapy, the destroyed bones recovered in correlation with the remission of the leukemia.[9, 21]

In the present case, the patient also complained of symptoms related to the shoulder joint at the time of the initial examination and was diagnosed with a fracture of the shoulder joint after a visit to an orthopedic surgeon. The shoulder joint fracture was also considered to have recovered because the infiltrating leukemia cells disappeared along with the remission of ALL.

It is generally known that jawbone resorbed by chronic marginal periodontitis does not recover.[22] However, in the case of jaw bone resorption associated with leukemia, there is a high possibility that the jaw bone will recover, as has been reported for the hands and feet.[23, 24]

Even in cases of severe bone resorption, as in the present case, there is a high likelihood of recovery with the remission of leukemia.

Although there are a few reports of extraction procedures performed on patients with ALL and tooth movement immediately after the onset of leukemia, there are cases in which the alveolar bone completely recovers, as seen in the present case.

In Japan, there are many case reports of patients with oral symptoms caused by leukemia, especially jaw bone resorption resulting in tooth movement, but there are no reports of cases in which highly resorbed jaw bone and tooth movement recovered with successful chemotherapy.

We report a case of a pediatric patient with ALL who had marked tooth movement and jaw bone resorption, whose jaw bone alveolar bone opacities on X-ray image increased with chemotherapy and remission of ALL. The tooth movement also resolved and occlusal function was restored.

Ethical approval

All investigations conducted on the patient were performed in accordance with the Declaration of Helsinki.

Author Contributions

Shinya Koshinuma and Takafumi Fujii: Conception and design of the study, acquisition, analysis and/or interpretation of data, and drafting of the manuscript

Takeshi Okamura: acquisition of data

Yasuyuki Asada: analysis and/or interpretation of data

Yoshisato Machida: revising the manuscript critically for important intellectual content

Gaku Yamamoto: Conception and design of the study, revising the manuscript critically for important intellectual content

All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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Figure and table legends

Fig 1 Dorsal foot, abdominal portrait

A: Photograph of the dorsal foot, B: Photograph of the abdomen

Scattered petechial hemorrhagic patches were observed on the dorsal surface of the foot and abdomen.

Fig 2 : Intraoral Photograph

A: Before treatment. Bleeding, redness, and swelling of the maxillary and maxillary gingiva were observed.

B: After treatment. All tooth movement, gingival hemorrhage, and gingival swelling resolved or improved, with no abnormalities in occlusion.

Fig 3 : Panoramic radiographs

A: Before treatment, B: After treatment

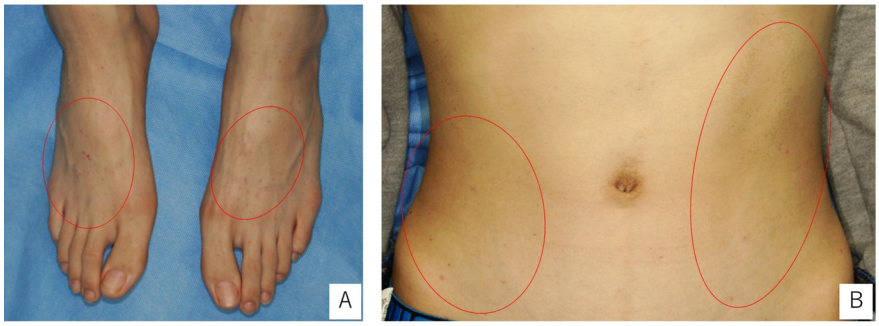
Fig 4 : Bone Marrow Test Results

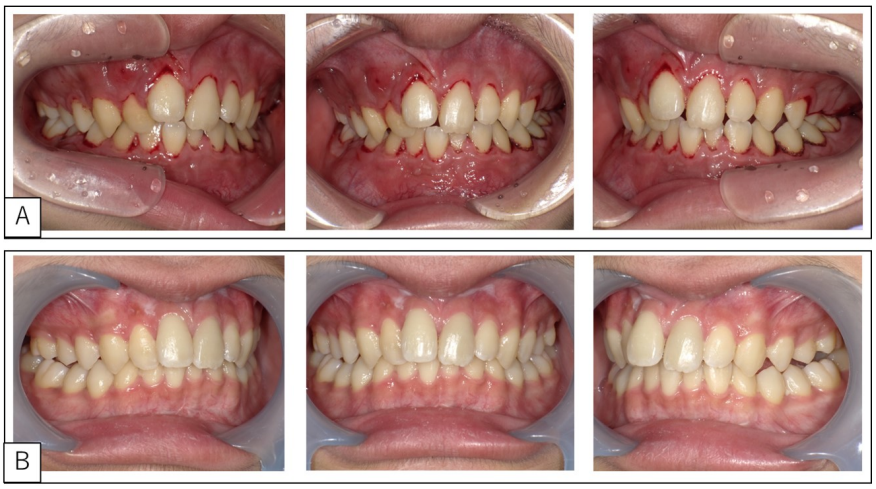
Bone marrow smear findings: Lymphoblast with medium to large vacuoles with a high nucleus/cytoplasm ratio of 75.8%(yellow arrow).

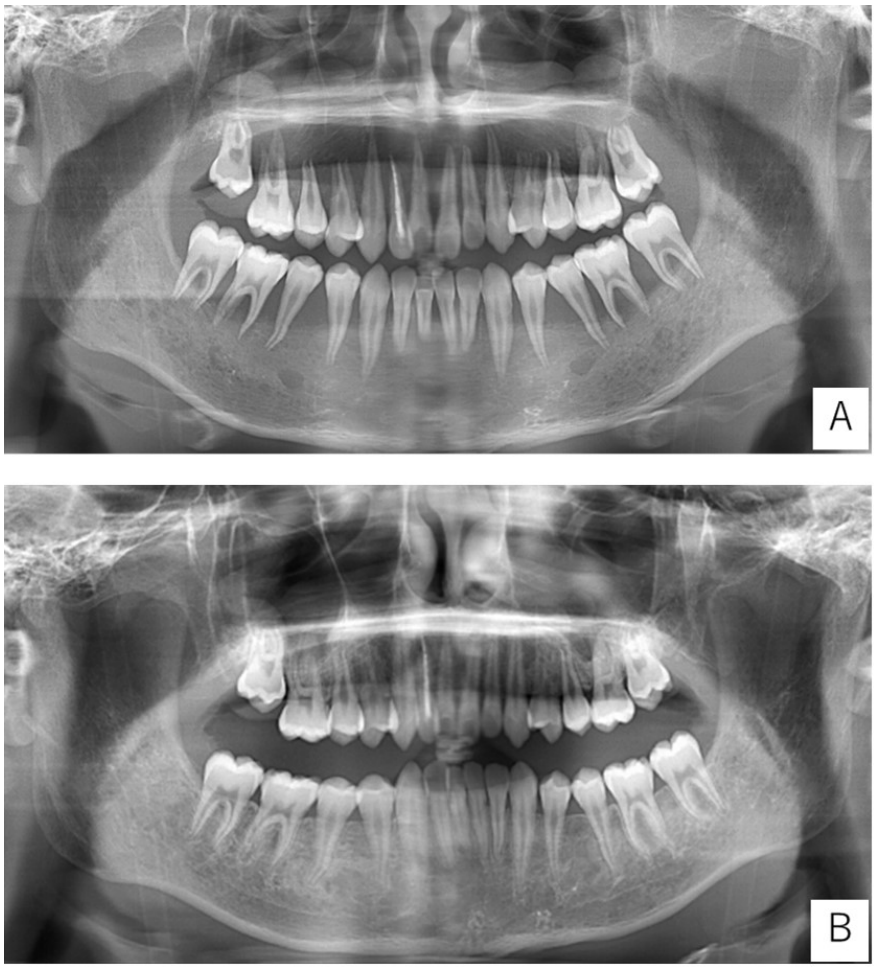
Table 1: Periodontal histology

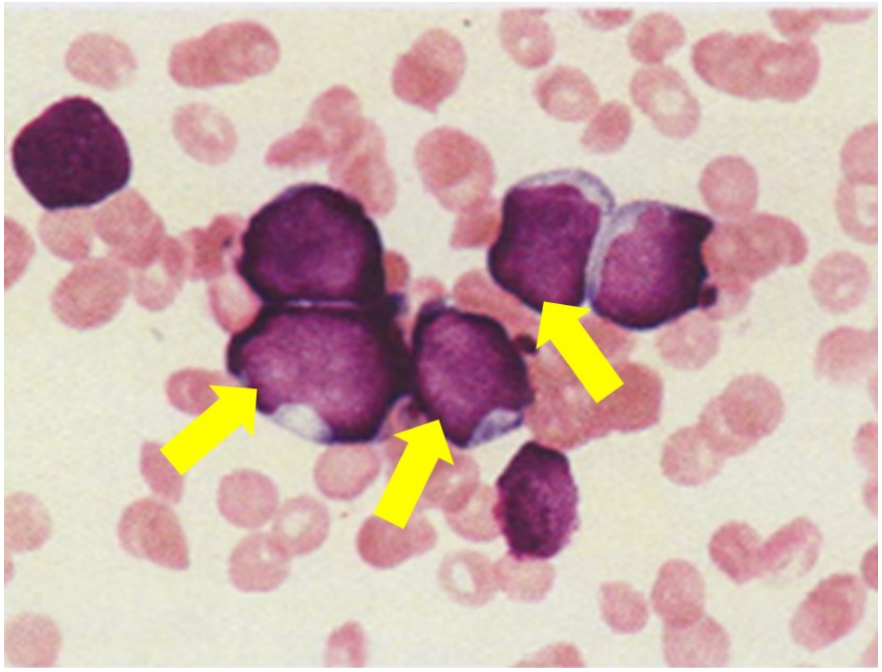
A: Before treatment. Periodontal pockets ranged from 3 to 9 mm, with the deepest at 9 mm. Significant tooth movement was observed in all jaws.

B: After treatment. Periodontal pockets were less than 3 mm in all jaws.









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